REMARKS

Claims 1, 2, 4-6, 8-22 and 25-34 were pending. Claim 22 is canceled herein without prejudice to its presentation in a divisional application. After entry of this amendment, **claims 1, 2, 4-6, 8-21 and 25-34 will be pending**.

Claims 12, 13, 17, and 34 are amended to correct minor typographical errors. Claim 26 is amended for clarity. The specification is amended to properly identify trademarks used in the application. No new matter has been introduced by these amendments and no amendments are made to distinguish prior art.

OBECTION TO THE SPECIFICATION

The Office objects to the specification for use of trademarked terms without proper identification. As required by the Office, all occurrences of Viracept and Crixivan have been capitalized to properly identify the terms as trademarks. Upon review of the specification, Applicants identified several additional trademarked terms. The specification is amended herein accordingly. Applicants believe all trademarked terms are now properly identified and request withdrawal of this objection.

REJECTION UNDER 35 U.S.C. § 112

Claim 22 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claim 22 is canceled herein as directed to non-elected subject matter, rendering the rejection moot. Applicants reserve the right to pursue the canceled subject matter in a divisional application.

REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1, 2, 6, 8-15, 21, 22, 26, 27 and 31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Klinman *et al.* (WO 00/61151), Lu *et al.* (*Vaccine* 15(8):920-923, 1997) and Cho *et al.* (*Nature Biotechnology* 18:509-514, 2000).

Claims 5 and 30 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Klinman *et al.*, Lu *et al.* and Cho *et al.*, in view of Yilma *et al.* (U.S. Patent No. 6,326,007) and Bieloria *et al.* (*Bone Marrow Transplantation* 26:1025-1028, 2000).

Claims 4, 16, 25, 28, 29 and 32 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Klinman *et al.*, Lu *et al.* and Cho *et al.*, in view of Raz *et al.* (U.S. Patent No. 6,552,006), Hamour *et al.* (*J. Infect.* 36(2):217-220, 1998, Abstract only) and Glaser *et al.* (*Clin. Infect. Dis.* 18(1):14-24, 1994, Abstract only).

Claims 17, 33 and 34 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Klinman *et al.*, Lu *et al.* and Cho *et al.*, in view of Davis *et al.* (*Vaccine* 18:1920-1924, 2000) and Chung *et al.* (*Antivir. Chem Chemother.* 12(1):73-91, 2001, Abstract only).

Claims 4 and 18-20 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Klinman *et al.*, Lu *et al.* and Cho *et al.*, in view of Hamour *et al.* and Fraternale *et al.* (*JAIDS* 23:209-220, 2000).

Applicants traverse each of these rejections for the reasons set forth below and for the reasons of record. Each of the above rejections under 35 U.S.C. § 103(a) relies upon the teachings of at least Klinman *et al.*, Lu *et al.* and Cho *et al.*. Therefore, the following arguments apply to all of the rejections.

A. *The Office has failed to establish a prima facie case of obviousness*

Contrary to the Office's assertion, previously cited U.S. Patent No. 6,077,245 to Klinman *et al.* is <u>not</u> the U.S. National Stage application of Klinman *et al.* (WO 06/61151), cited in the current Office action. Rather, U.S. Patent No. 6,077,245 is a <u>continuation-in-part</u> application of the U.S. National Stage application of Klinman *et al.*, and therefore contains additional teachings not found in WO 06/61151. On page 4 of the current Office action, the Office summarizes the teachings of Klinman *et al.* (WO 06/61151). The Office alleges that this reference teaches immunostimulatory D oligodeoxynucleotides having a sequence represented by the formula $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M(G)_N$ and cites several locations in the publication where these teachings can supposedly be found. However, Applicants respectively point out that Klinman *et al.* (WO 06/61151) is <u>not</u> equivalent to U.S. Patent No. 6,077,245, therefore the cited passages do not correspond to the text of Klinman *et al.* (WO 06/61151). Moreover, upon review of Klinman *et al.* (WO 06/61151), the formula $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M(G)_N$ is not disclosed anywhere in Klinman *et al.* (WO 06/61151).

The Office asserts that Klinman *et al.* (WO 06/61151) teaches the structure of the immunostimulatory sequence recited in the pending claims, but admits that this reference does not teach a method of increasing an immune response to an opportunistic infection in an immunocompromised subject having a secondary viral infection (see page 4 of the Office action). To establish a *prima facie* case of obviousness, the Office relies upon Lu *et al.* and Cho *et al.* as allegedly teaching opportunistic infections in SIV-infected animals and immunostimulatory DNA sequences in subjects with chronic immunosuppression. However, as noted above, Klinman *et al.* (WO 06/61151) does not teach the oligonucleotide structure ($X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M$ $(G)_N$) recited in claim 1. Even if for the sake of argument, Klinman *et al.* is considered to teach the oligonucleotide structure recited in claim 1, the combination of cited references still does not teach each and every element of the pending claims.

As admitted by the Office, Klinman *et al.* do not teach a method of increasing an immune response to an opportunistic infection in an immunocompromised subject. In particular, because Klinman *et al.* do not teach or even suggest immunocompromised subjects or subjects with secondary infections, this reference does not teach the steps of selecting an immunocompromised subject with a secondary infection and assessing the immune response to the secondary infection. Neither Lu *et al.* nor Cho *et al.* cure these deficiencies.

Lu *et al.* is cited only as teaching that secondary infections can occur in immunocompromised subjects, such as those infected with a retrovirus. Lu *et al.* do not teach or suggest selecting an immunocompromised subject with a secondary infection. Rather, this reference teaches vaccination of <u>healthy</u> animals, which were subsequently challenged with SIV. Some of the vaccinated animals, in addition to the unvaccinated animals, developed opportunistic infections following virus challenge. The authors of the Lu *et al.* reference merely note the presence or absence of the opportunistic infection and therefore do not teach assessing an immune response to a secondary infection as recited in the pending claims.

Similarly, Cho *et al.* do not teach or suggest the method steps recited in the instant claims. Cho *et al.* describe vaccination of <u>healthy</u> animals with an immunostimulatory DNA sequence conjugated to ovalbumin and evaluating CTL activity and cytokine production in response to the vaccine. In addition, the authors test the ability of the vaccine to protect animals

against subsequent lethal tumor challenge. The animals in this study were not immunocompromised and did not have secondary infections. Moreover, there is no teaching in this reference of evaluating an immune response to a secondary infection. Cho *et al.* state that the disclosed vaccines "may have another clinical application in AIDS and other immunodeficiencies, which are characterized by reduced or absent T_h function. These vaccines could induce effective cell-mediated immunity independent of T-cell help, providing protection against opportunistic infection" (see page 513, left column, second full paragraph; emphasis added). Thus, the authors merely postulate that a vaccine comprising an immunostimulatory DNA sequence could be used to treat an immunocompromised subject, without providing any evidence that such vaccines would be effective.

In summary, the combination of cited references does not teach or even suggest (1) selecting an immunocompromised subject infected with a secondary infection; (2) administering to the subject a therapeutically effective amount of a oligonucleotide of the formula $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M(G)_N$; or (3) assessing the immune response to the secondary infection in the subject, as recited in claim 1 (and required by dependent claims 2, 4-6, 8-21, 26, 27 and 30-34). In regard to independent claim 25 (and dependent claims 28 and 29), the combination of cited references does not teach or suggest the step of selecting an immunocompromised subject. Applicants further note that the additional secondary references cited by the Office in support of the above-listed rejections under 35 U.S.C. §103(a) do not teach or suggest any of the these method steps. The secondary references are cited merely for teaching particular types of secondary infections[1] or types of anti-retroviral therapies.[2] Accordingly, the Office has failed to establish a *prima facie* case of obviousness against any of the pending claims.

B. The claimed methods exhibit unexpectedly superior results

Even if a *prima facie* case of obviousness is maintained, the claimed methods provide unexpectedly superior results, as discussed at length in the responses filed January 2, 2009 and July 17, 2009. For the Examiner's convenience, some of the prior arguments are summarized below.

[1] Yilma *et al.*, Bieloria *et al.*, Raz *et al.*, Hamour *et al.*, Glaser *et al.*, Davis *et al.* and Chung *et al.*
[2] Fraternale *et al.*

Pages 4-5 of the Declaration under 37 C.F.R. § 1.132 (submitted with the response filed on June 5, 2008) describe the results obtained when D oligodeoxynucleotides were evaluated in an art-accepted macaque model of HIV. Macaques that had been infected for greater than 12 months with SIV Mac239, and had viral loads ranging from 0.3-28 x 10^6 copies/ml, were used in these studies. The animals were stratified based on viral load and then challenged with *L. major* metacyclic promastigotes (MHOM/IL/80/Friedlin), which is a secondary infection. Healthy macaques challenged with *L. major* developed cutaneous lesions characterized by erythema, induration and ulceration that peaked 25 days after challenge and resolved within 50 days (see Fig. 3A of the Declaration). Due to their immunosuppressed state, untreated macaques developed severe progressive cutaneous lesions that did not resolve. The severity of *Leishmania* infection in SIV-infected animals treated with K oligodeoxynucleotide (ODN) was not significantly different from that of the controls.

In contrast, SIV-infected macaques treated with D ODN developed significantly smaller lesions, and their infection did not progress over time (Fig. 3A of the Declaration) as compared to controls. The animals were euthanized on day 56, and their parasite burden measured. SIV-infected monkeys treated with D ODN had a 35-fold reduction in total parasite burden at the lesion site compared to SIV-infected animals treated with control ODN or saline (see Fig. 3B of the Declaration, $p<0.001$). The comparative data, both with regard to the type of ODN used (D versus K), and the type of immune response achieved (general response versus a response to a secondary infection) demonstrate the unexpectedly superior result that is achieved using the claimed methods.

The documentation of an unexpectedly superior result overcomes any *prima facie* case of obviousness based on the cited references.

C. Conclusion

For at least the reasons detailed above, Applicants submit the pending claims are not obvious in view of the cited references. Accordingly, Applicants request withdrawal of these rejections under 35 U.S.C. §103(a).

CONCLUDING STATEMENT

It is respectfully submitted that the present claims are in a condition for allowance. Should the Examiner have further questions or comments with respect to examination of this case, it is respectfully requested that the Examiner telephone the undersigned so that further examination of this application can be expedited.

Respectfully submitted,

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